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Ticlopidine-Induced Aplastic Anemia and Quick Recovery With G-CSF: Case Report and Literature Review

A. Taher,* Z. Ammash, B. Dabajah, A. Nasrallah, and F. H. Mourad

Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

We report here a case of ticlopidine-induced aplastic anemia that responded to G-CSF and review the literature. An 83-year-old woman was started on ticlopidine for coronary artery disease after an episode of upper gastrointestinal bleeding secondary to aspirin. She developed aplastic anemia seven weeks after initiation of ticlopidine. She was hospitalised and received empiric antibiotic therapy and granulocyte colony stimulating factor (G-CSF). Her bone marrow started to recover quickly, and white blood cell and platelet counts returned to normal within three weeks. A review of medical literature revealed 20 similar cases of ticlopidine-induced aplastic anemia resulting in death in seven cases. G-CSF has been used previously with variable success. Ticlopidine is associated with serious, sometimes fatal hematological side effects. This risk should be seriously taken into consideration when prescribing ticlopidine. G-CSF may be helpful in the treatment of ticlopidine-induced aplastic anemia. Am. J. Hematol. 63:90–93, 2000.

Key words: ticlopidine; aplastic anemia; G-CSF

INTRODUCTION

Ticlopidine, an inhibitor of platelet aggregation, has been used during the past several years for prevention of diseases in which thromboembolism is thought to play a role [1]. Hematological toxicity is one of the most important side effects of ticlopidine, including neutropenia, thrombocytopenia, pancytopenia, hemolytic anemia, thrombotic thrombocytopenic purpura, and more seriously aplastic anemia [2]. We report a case of ticlopidine-associated aplastic anemia with quick and full recovery after discontinuation of the drug and treatment with granulocyte colony stimulating factor (G-CSF).

CASE REPORT

An 83-year-old woman, known to have coronary artery disease, chronic renal failure, and ascending aortic aneurysm, was admitted to the hospital in May 1995 with pulmonary edema and chest pain. Investigation revealed WBC = 1.3×10^9/l, Hct = 29%, platelets = 153×10^9/l, and serum creatinine = 3.3 mg/dl. She was previously maintained on aspirin and was then shifted to ticlopidine at a dose of 250 mg twice/day orally after an upper gastrointestinal bleed seven weeks prior to the present admission. At that time, her blood tests revealed mild anemia and uremia but normal WBC and platelet counts (WBC = 8.2×10^9/l, Hct = 31%, platelets = 244×10^9/l, serum creatinine = 2.5 mg/dl). No blood tests were performed over this time interval, but she was clinically well with no symptoms. There was no history of viral infection, and there was no history of drug intake other than Moduretic® (amiloride hydrochloride and hydrochlorothiazide), diltiazem, and ticlopidine. Bone marrow aspirate was almost completely devoid of all marrow elements (aplastic marrow), iron stain showed adequate stores, and no ringed sideroblasts were seen. Ticlopidine-induced leukopenia was suspected, the drug was immediately stopped, but the WBC count continued to decline. Three days after admission, her WBC count dropped to

*Correspondence to: Ali Taher, MD, American University of Beirut Medical Center, P.O. Box 113-6044, Beirut, Lebanon. E-mail: ataher@aub.edu.lb

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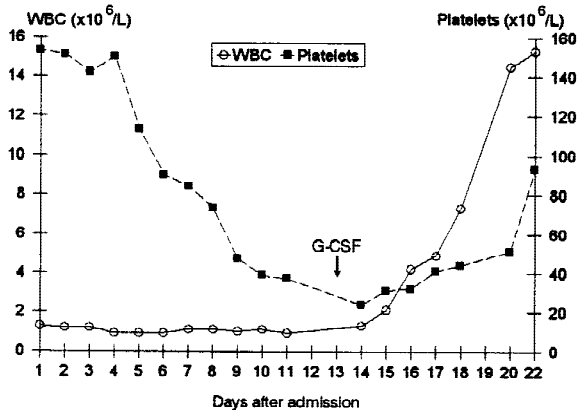

Fig. 1. Time course of white blood cells and platelet count after stopping ticlopidine and the effect of G-CSF administration.

0.9×10^9/liter, and she developed high-grade fever secondary to left lower lobe pneumonia as shown on a chest X-ray. She was started on ceftazidime, and she defervesced within a few days. For 11 days after stopping ticlopidine, the WBC count stabilised at $(0.9–1.1) \times 10^9$/l (Fig. 1). Platelet count started to drop five days after admission, reaching a nadir of 37×10^9/l on day 11 (Fig. 1). At that moment, it was decided to start the patient on granulocyte colony stimulating factor (G-CSF, Neupogen®) at a dose of 5 μg/kg sc daily. The hematological profile improved markedly within a few days, and one week later the WBC count returned to normal values, and the platelet count reached 93×10^9/liter.

The patient was discharged home 23 days after admission to the hospital in good general condition on erythropoietin for her renal failure-induced anemia in addition to her cardiac medications. A follow-up CBC one week later revealed a WBC = 8.3×10^9/l, Hct = 34%, and platelet count = 150×10^9/l.

DISCUSSION

Ticlopidine is an antiplatelet aggregration agent that was introduced as a preventive drug in thromboembolic associated diseases. Its main mode of action is to inhibit the effect of ADP on activation of platelet membrane glycoprotein [1]. Ticlopidine is totally absorbed after an oral dose, extensively metabolised in the liver, and approximately 60% excreted in the urine. Plasma levels of the drug are significantly higher, and metabolic clearance is significantly lower in elderly subjects [3], and this may increase the risk of side effects in these subjects who are the main target for ticlopidine use. Many side effects have been reported with ticlopidine treatment, such as diarrhea, dyspepsia, dizziness, and headache. A more dangerous and fortunately less frequent side effect is hematological toxicity, such as neutropenia, thrombocytopenia, thrombotic thrombocytopenic purpura, and aplastic anemia [2]. The latter is the most serious side effect, which is being reported more frequently in recent years with the widespread use of ticlopidine [4–19]. Twenty patients of a mean age of 70.3 years (range: 51–85) have been reported in the literature as having developed aplastic anemia secondary to ticlopidine (Table I). The mean time interval between starting the treatment and the appearance of the side effect was 10.6 weeks (range: 3–73) and a median of six weeks (Table I). Most patients presented with fever and anemia, and only two reported cases were discovered to be pancytopenic on routine checkup [13,14]. The time to recovery was as short as three weeks [12,13] and as protracted as 52 weeks [5]. Death was not infrequent and occurred in seven patients one day to 21 weeks after presentation and drug discontinuation [6–8,10,11,16,17]. In general, treatment was mostly supportive and colony stimulating factor was tried in eight reported cases with variable success [6–9,11–13]. Four of those patients recovered 4 to more than 13 weeks after stopping ticlopidine [9,12,13], and four patients died after 1–21 weeks [6–8,11] following cessation of ticlopidine therapy despite administration of colony stimulating factor.

This patient was at a high risk of developing ticlopidine-related side effects. She was an 83-year-old woman in whom the steady state trough concentration of ticlopidine is estimated to be twice that of young volunteers [20]. In addition, she had renal impairment that led to a decrease in drug clearance. Ticlopidine was incriminated as the cause of her aplastic anemia as the other two drugs she was taking are not known to have this side effect. The hematological toxicity occurred seven weeks after starting ticlopidine, which is similar to what is described in literature, and white blood cells were the first elements to show a significant decrease. This patient responded dramatically to G-CSF, with a quick recovery of WBC and platelet count and normalization of the blood profile within 23 days.

The mechanism of ticlopidine toxicity is not fully understood. A proposed mechanism has been offered by Ono et al. [21], who evaluated a single patient who developed agranulocytosis after 30 days of ticlopidine therapy. Following recovery from neutropenia, a culture of this patient's bone marrow depleted of lymphocytes was exposed to various concentrations of ticlopidine in vitro. When compared with similarly derived cultures from control subjects, the findings indicated that ticlopidine directly inhibited the colony forming unit in culture in a concentration-dependent manner in the patient who experienced neutropenia. This effect was not seen in the controls, proving that ticlopidine has a direct toxic effect

TABLE I. Characteristics, Symptoms, Treatment, and Outcome of Cases of Ticlopidine-induced Aplastic Anemia Reported in the Literature*

Reference[a]	Age/sex	Symptoms	*t* after start (weeks)	Treatment	*t* to R or D (weeks)
Garnier et al. (1992)[4]	74/M	Fever, wasting	6	Supportive	8 R
Troussard et al. (1992)[5]	73/F	Fever	8	Androgens	43 R
Troussard et al. (1992)[5]	66/F	Fever, bruising, cholestasis	22	Androgens	52 R
Khelif et al. (1993)[6]	61/F	Fever, abdominal pain, diarrhea	9	Supportive	5 R
Khelif et al. (1993)[6]	79/M	Fever	6	GM-CSF	1 D
Mallet et al. (1994)[7]	84/F	Fever	6	G-CSF	11 D
Rodriguez et al. (1994)[8]	69/M	Fever, odynophagia	8	G-CSF, steroids	3 D
Lesesve et al. (1994)[9]	51/M	Fever, fatigue	10	Supportive	7 R
Lesesve et al. (1994)[9]	69/M	Fatigue, amygdalitis	8	G-CSF, steroids	>13 R
Su et al. (1995)[10]	85/F	Chills, fever	5	Supportive	2 D
Arribalzaga et al. (1995)[11]	78/M	Fever	6	G-CSF	21 D
Dunn (1996)[12]	66/F	Fever	6	G-CSF	4 R
Dunn (1996)[12]	67/F	Fever	6	G-CSF	3 R
Shapiro et al. (1996)[13]	80/F	Routine checkup	5	G-CSF Erythropoietin	6 R
Green (1997)[14]	53/M	Routine checkup	73	Antithymocyte globulin	12 R
Elias et al. (1993)[15]	64/F	Sore throat, fever	4	Supportive	3 R
Carlston et al. (1994)[16]	83/M	Confusion, odynophagia	8	Supportive	1/7 D
Martin-Nunez et al. (1993)[17]	66/F	Fever, anemia, diarrhea	6	Supportive	4/7 D
Mataix et al. (1992)[18]	67/F	Fever, anemia, bruising	3	Steroids	8 R
Weiner et al. (1995)[19]	73/F	Fever, vaginal bleeding	8	Steroids	8 R

*t = time; R = recovery; D = death.
[a]Reference numbers are superscripts 4–19 in this column.

on the bone marrow of susceptible subjects. In addition, Yunis et al. [22] found that ticlopidine inhibits in vitro myeloid colony (CFU-GM) growth, suggesting that the effect of the drug is directly toxic to the bone marrow cells rather than an idiosyncratic one. This effect could be assigned to an increase in the prostaglandin E_1 (PGE_1) synthesis directly produced by this drug [23]. On the other hand, an immunologic mechanism for pancytopenia has also been suggested [24].

Assuming that ticlopidine has a direct inhibitory effect on CFU-GM, then G-CSF would be a logical treatment in patients with ticlopidine-induced aplastic anemia. However, its use in the literature, though limited, is not very encouraging, as many patients had persistence of bone marrow suppression [6–9,11], leading to death in a few instances [6–8,11]. This patient responded dramatically to G-CSF with quick recovery of granulocytes and platelets. The use of G-CSF to treat ticlopidine-induced agranulocytosis needs to be further investigated. However, because of the serious complications associated with an aplastic marrow, colony stimulating factors should be given as a trial to such patients.

In conclusion, ticlopidine is an effective antiplatelet drug but is associated with serious, sometimes fatal hematological side effects. Thus, this risk should be weighed when choosing ticlopidine, and it should be reserved for patients who are not able to tolerate aspirin. Patients receiving ticlopidine therapy should be closely

monitored for signs and symptoms of hematological toxicity.

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